Also included are the membrane-anchored ADAMs (**A Disintegrin And Metalloproteinase**), which are multimeric molecules consisting of metalloproteinase, disintegrin-like, cysteine rich, and epidermal growth factor domains. *See* Black, R.A. and White, J.M., (1998) "ADAMs: focus on the protease domain," Curr Opin Cell Biol 10, 654-659 (in process); Wolfsberg, T.G. and White, J.M. (1996) "ADAMs in fertilization and development," Dev Bio 180, 389-401, all of which are herein incorporated by reference. The ADAMs family includes fertilin-α and meltrin-α, both of which are involved in membrane or cell-cell fusion. Specifically, the disintegrin domain of fertilin-α and meltrin-α have been implicated in sperm/egg fusion and myoblast fusion, respectively.

Please replace the paragraph at page 2, lines 18-27, with the following rewritten paragraph:

ADAMS 1-6 have been implicated in fertilization and/or spermatogenesis (Barker, H.L., Perry, A.C., Jones, R., and Hall, L., *Biochim Biophys Acta*, 1218, 429-31, 1994; Blobel, C.P., Wolfsberg, T.G., Turck, C.W., Myles, D.G., Primakoff, P., and White, J.M., *Nature*, 356, 248-252, 1992; Evans, J.P., Schultz, R. M., and Kopf, G.S., *J. Cell Sci*, 108, 3267-3278, 1995; Perry, A.C., Barker, H.L., Jones, R., and Hall, L., *Biochim Biophsy Acta*, 1207, 134-137, 1994; Perry, A.C., Gichuhi, P.M., Jones, R., and Hall, L., *Biochem J.*, 307, 843-850, 1995; Perry, A. C., Jones, R., and Hall, L., *Biochem J.*, 312, 239-244, 1995; Wolfsberg, T.G., Bazan, J.F., Blobel, C.P., Mules, D. G., Primakoff, P., and White, J.M., *Proc Natl Acad Sci USA*, 90, 10783-10787, 1993; and Wolfsberg, T.G., Straight, P.D., Gerena, R.L., Huovila, A.P., Primakoff, P., Myles, D.G., and White, J. M., *Dev Biol*, 169, 378-383, 1995).

Please replace the paragraphs at page 4, line 12 through page 5, line 5 with the following rewritten paragraphs:

In addition, when a peptide fingerprint of an unknown protein is obtained, it can be compared to a database of known proteins to assist in the identification of the unknown protein using mass spectrometry (W.J. Henzel et al., *Proc. Natl. Acad. Sci. USA* 90:5011-5015, 1993; D. Fenyo et al., *Electrophoresis* 19:998-1005, 1998). A variety of computer software programs to facilitate these comparisons are accessible

via the Internet, such as Protein Prospector (prospector.uscf.edu), MultiIdent (expasy.ch/sprot/multiident), PeptideSearch (mann.embl-heiedelberg.de...deSearch/FR_PeptideSearch Form), and ProFound (chait-sgi.rockefeller.edu/cgi-bin/prot-id-frag). These programs allow the user to specify the cleavage agent and the molecular weights of the fragmented peptides within a designated tolerance. The programs compare these molecular weights to protein molecular weight information stored in databases to assist in determining the identity of the unknown protein. Accurate information concerning the number of fragmented peptides and the precise molecular weight of those peptides is required for accurate identification. Therefore, increasing the accuracy in determining the number of fragmented peptides and their molecular weight should result in enhanced likelihood of success in the identification of unknown proteins.

B4 cont

In addition, peptide digests of unknown proteins can be sequenced using tandem mass spectrometry (MS/MS) and the resulting sequence searched against databases (J.K. Eng, et al., *J. Am. Soc. Mass Spec.* 5:976-989 (1994); M. Mann and M. Wilm, *Anal. Chem.* 66:4390-4399 (1994); J.A. Taylor and R.S. Johnson, *Rapid Comm. Mass Spec.* 11:1067-1075 (1997)). Searching programs that can be used in this process exist on the Internet, such as Lutefisk 97 (lsbc.com:70/Lutefisk97), and the Protein Prospector, Peptide Search and ProFound programs described above. Therefore, adding the sequence of a gene and its predicted protein sequence and peptide fragments to a sequence database can aid in the identification of unknown proteins using tandem mass spectrometry.

Please replace the paragraph at page 11, lines 18-21, with the following rewritten paragraph:

B5

SVPH3-13 and 3-17 proteinases are members of the snake venom protease family. SVPH3-13 (ADAM22) polypeptide (SEQ ID NO:3) encodes a portion of the disintegrin domain. SVPH3-13 (ADAM22) DNA (SEQ ID NO:5) encodes an SVPH3-13 (ADAM22) polypeptide (SEQ ID NO:6), which lacks a portion of the amino terminal signal sequence.

Please replace the paragraph at page 12, lines 2-4, with the following rewritten paragraph:

B6

SVPH3-13 (ADAM22) is specifically expressed in brain by Northern analysis (Example 1). SVPH3-17 (ADAM23) is specifically expressed in brain and heart by Northern analysis (Example 1). Therefore, SVPH3-13 and SVPH3-17 may be involved in neurogenesis.

Please replace the paragraph at page 13, lines 15-27, with the following rewritten paragraph:

B7

In a particular embodiment, the invention relates to certain isolated nucleotide sequences that are free from contaminating endogenous material. A "nucleotide sequence" refers to a polynucleotide molecule in the form of a separate fragment or as a component of a larger nucleic acid construct. The nucleic acid molecule has been derived from DNA or RNA isolated at least once in substantially pure form and in a quantity or concentration enabling identification, manipulation, and recovery of its component nucleotide sequences by standard biochemical methods (such as those outlined in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY (1989)). Such sequences are preferably provided and/or constructed in the form of an open reading frame uninterrupted by internal non-translated sequences, or introns, that are typically present in eukaryotic genes. Sequences of non-translated DNA can be present 5' or 3' from an open reading frame, where the same do not interfere with manipulation or expression of the coding region.

Please replace the paragraph at page 39, lines 16-19, with the following rewritten paragraph:

B8

Similarly, all or a portion of the nucleic acids of SEQ ID 2, including oligonucleotides, can be used by those skilled in the art using well-known techniques to identify the human chromosome 2, and the specific locus 2q33, that contains the DNA of SVPH3-17 (ADAM23) family members.

Please replace the paragraph at page 39, line 25 through page 40, line 4 with the following rewritten paragraph:

B9

For example, chromosomes can be mapped by radiation hybridization. First, PCR is performed using the Whitehead Institute/MIT Center for Genome Research Genebridge4 panel of 93 radiation hybrids (genome.wi.mit.edu/ftp/distribution/human_STS_releases/july97/rhmap/genebridge4). Primers are used which lie within a putative exon of the gene of interest and which amplify a product from human genomic DNA, but do not amplify hamster genomic DNA. The results of the PCRs are converted into a data vector that is submitted to the Whitehead/MIT Radiation Mapping site on the internet (seq.wi.mit.edu). The data is scored and the chromosomal assignment and placement relative to known Sequence Tag Site (STS) markers on the radiation hybrid map is provided. The following web site provides additional information about radiation hybrid mapping: genome.wi.mit.edu/ftp/distribution/human_STS_releases/july97/ 07-97.INTRO).

Please replace the paragraph at page 47 line 24 to page 48, line 3, with the following rewritten paragraph:

B10

Similarly, these reagents can be used to investigate constitutive and transient expression of SVPH3-13 (ADAM22) or 3-17 (ADAM23) RNA or polypeptides. SVPH3-13 (ADAM22) and 3-17 (ADAM23) DNAs can be used to determine the chromosomal location of SVPH3-13 and 3-17 DNAs and to map genes in relation to this chromosomal location. SVPH3-13 and 3-17 DNAs can also be used to examine genetic heterogeneity and heredity through the use of techniques such as genetic fingerprinting, as well as to identify risks associated with genetic disorders. SVPH3-13 and 3-17 DNAs can be further used to identify additional genes related to SVPH3-13 or 3-17 DNAs and to establish evolutionary trees based on the comparison of sequences. SVPH3-13 and 3-17 DNAs and polypeptides can be used to select for those genes or proteins that are homologous to SVPH3-13 or 3-17 DNA or polypeptides, through positive screening procedures such as Southern blotting and immunoblotting and through negative screening procedures such as subtraction.

Please replace the paragraphs at page 58, line 18 through page 59, line 5 with the following rewritten paragraphs:

As set forth above, a polypeptide or peptide fingerprint can be entered into or compared to a database of known proteins to assist in the identification of the unknown protein using mass spectrometry (W.J. Henzel et al., Proc. Natl. Acad. Sci. USA 90:5011-5015, 1993; D. Fenyo et al., Electrophoresis 19:998-1005, 1998). A variety of computer software programs to facilitate these comparisons are accessible via the Internet, such as Protein Prospector (prospector.uscf.edu), MultiIdent (expasy.ch/sprot/multiident), PeptideSearch (mann.embl-heiedelberg.de...deSearch/FR_PeptideSearch Form), and ProFound (chait-sgi.rockefeller.edu/cgi-bin/prot-id-frag). These programs allow the user to specify the cleavage agent and the molecular weights of the fragmented peptides within a designated tolerance. The programs compare observed molecular weights to predicted peptide molecular weights derived from sequence databases to assist in determining the identity of the unknown protein.

B11

In addition, a polypeptide or peptide digest can be sequenced using tandem mass spectrometry (MS/MS) and the resulting sequence searched against databases (J.K. Eng, et al., J. Am. Soc. Mass Spec. 5:976-989 (1994); M. Mann and M. Wilm, Anal. Chem. 66:4390-4399 (1994); J.A. Taylor and R.S. Johnson, Rapid Comm. Mass Spec.11:1067-1075 (1997)). Searching programs that can be used in this process exist on the Internet, such as Lutefisk 97 (sbc.com:70/Lutefisk97), and the Protein Prospector, Peptide Search and ProFound programs described above.

Please replace the paragraph at page 59, lines 20-30, with the following rewritten paragraph:

These antigenic determinants or epitopes can be either linear or conformational (discontinuous). Linear epitopes are composed of a single section of amino acids of the polypeptide, while conformational or discontinuous epitopes are composed of amino acids sections from different regions of the polypeptide chain that are brought into close proximity upon protein folding (C. A. Janeway, Jr. and P. Travers, *Immuno Biology* 3:9 (Garland Publishing Inc., 2nd ed. 1996)). Because folded proteins have complex surfaces, the number of epitopes available is quite

B12

numerous; however, due to the conformation of the protein and steric hindrances, the number of antibodies that actually bind to the epitopes is less than the number of available epitopes (C. A. Janeway, Jr. and P. Travers, *Immuno Biology* 2:14 (Garland Publishing Inc., 2nd ed. 1996)). Epitopes may be identified by any of the methods known in the art.

B12 Cont

Please replace the paragraph at page 64, lines 15-18, with the following rewritten paragraph:

B13

Chromosomal mapping of SVPH3-13 and SVPH3-17 was performed by radiation-hybrid mapping (Walter *et al.*, 1994). The GeneBridge 4 radiation-hybrid mapping panel (Research Genetics, Huntsville, AL) was screened with specific primer pairs for SVPH3-13 (ADAM22) and SVPH3-17 (ADAM23).

IN THE CLAIMS:

Please cancel claims 17-20 and 24-29 without prejudice to present such claims in a subsequent application.

Please amend claims 15 and 22-23 as shown by the following rewritten claims:

B14

15 (amended). An isolated nucleic acid molecule selected from the group consisting of:

(a) a nucleic acid molecule having the sequence of SEQ ID NO:2;

(b) a nucleic acid molecule encoding an amino acid sequence comprising the sequence of SEQ ID NO:4;

(c) a nucleic acid molecule that encodes a fragment of the polypeptide of SEQ ID NO:4 having disintegrin activity;

(d) a nucleic acid molecule encoding a fragment of the amino acid sequence of SEQ ID NO:4 having disintegrin activity and comprising amino acids 496-599 of SEQ ID NO:4; and